DETAILED ACTION

Status of the claims: Claims 1-26 are currently pending.

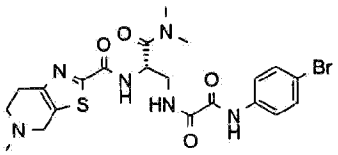
Priority: This application is a 371 of PCT/JP03/16556 (12/24/2003) and claims foreign priority to JAPAN 2002-373025 (12/24/2002). A certified copy of the foreign priority document is not of record as required by 35 USC 119(a-d).

IDS: The IDS dated 6/22/05, 9/6/05, 11/30/05, and 7/28/09 were considered.

Election/Restrictions

1. Applicant's election without traverse of group I (claims 1-19) in the reply filed on 3/30/10 is acknowledged. Applicant also elected the following species reading on claims 1-3, 7-9, and 11-19:

[Example 38] N^1-(4-Bromophenyl)-N^2-((2S)-3-(dimethylamino)-2-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]amino}-3-oxopropyl)ethanediamide hydrochloride



As detailed in the following rejections, the generic claim encompassing the elected species was not found patentable. Therefore, the provisional election of species is given effect, the examination is restricted to the elected species only, and claims not reading on the elected species are held withdrawn. Accordingly, claims 4-6, and 10 are hereby withdrawn.

Should applicant, in response to this rejection of the Markush-type claim, overcome the rejection through amendment, the amended Markush-type claim will be reexamined to the extent necessary to determine patentability of the Markush-type claim. See MPEP 803.02.

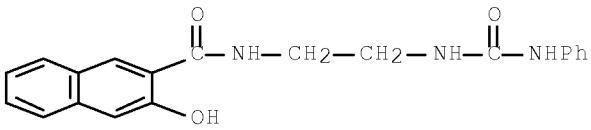
Claim Rejections - 35 USC § 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Claims 1-3, 7, 9, and 11-13 are rejected under 35 U.S.C. 102(b) as being anticipated by Matsuda (CAPLUS abstract of JP 09152677).

The prior art teaches the following compound which anticipates the claims:



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when Q1 is naphthalene substituted by hydroxyl, Q2 is a bond, T0 is a carbonyl, R1 and R2 are H, Q3 is -CH2-CH2-, T1 is –C(O)-N(H)-, and Q4 is Ph.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-3, 7-9, and 11-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject

matter which applicant regards as the invention. The claims use language such as "which may have a substituent" without clearly defining what structural limitations this corresponds to. Although applicant provides exemplary language for some of the "substituents," this does not clearly define the metes and bounds of the claim such that one of ordinary skill in the art could determine whether they would infringe the claims. See MPEP §2173.05(d).

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-3, 7-9, and 11-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the compounds identified as having inhibitory effect with IC50 data, does not reasonably provide enablement for the asserted utility of the entirety of the claim scope. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Particularly relevant to the instant case is the issue as to whether the specification provides embodiments allowing use of the claimed invention without requiring undue experimentation by one of ordinary skill in view of the highly unpredictable nature of inhibiting enzymes.

> "[An inventor] must not be permitted to achieve . . . dominance by claims which are insufficiently supported and hence not in compliance with the first paragraph of 35 U.S.C. 112. That paragraph requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. In cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad

> enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved." *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

Accordingly, the critical element here how broad the claims are compared to the level of unpredictability in the art.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the specification coupled with information known in the art without undue experimentation (*United States v. Telectronics*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is needed is not based upon a single factor but rather is a conclusion reached by weighing many factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int. 1986) and again in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) and include the following:

Nature of Invention. The nature of the invention involves pharmaceutical compounds for inhibiting enzymes.

Scope of the Invention. The scope of the invention are for a genus of compounds of formula I ($Q^1-Q^2-T^o-N(R^1)-Q^3-N(R^2)-T^1-Q^4$) having in excess of billions of species.

State of the Art and Level of Skill in the Art. Although the level of skill in the art is very high, inhibiting enzymes is a very unpredictable art. Kubinyi (3D QSAR in Drug Design: Ligand-Protein Interactions and Molecular Similarity, Vol 2-3, Springer, 1998, 800 pages) teaches that very slight perturbations in the structure of an inhibitor (such as the addition of a methyl group or inversion of a chiral center, see p. 243) can have radical effects on the binding of an inhibitor. In addition, specifically in the context of FXa inhibitors, Zhao et al. (Bioorganic & Medicinal Chemistry Letters 10 (2000) 963-966) teaches several tables where the activities of inhibitors vary substantially with only minor changes in structure.

Number of Working Examples and Guidance Provided by Applicant. The applicant provides a one paragraph listing in vitro IC50 values for human FXa for 8 compounds (on page 566 of the specification) as shown below:

> From the test results that IC.sub.50 of the compound of Example 2 is 7.1 nM, that of the compound of Example 26 is 2.4 nM, that of the compound of Example

> 37 is 1.5 nM, that of the compound of Example 38 is 0.81 nM, that of the compound of Example 39 is 0.86 nM, that of the compound of Example 40 is 1.3 nM, that of the compound of Example 62 is 1.8 nM and that of the compound of Example 66 is 2.0 nM, it has been elucidated that the compounds according to the invention have a potent FXa inhibitory action.

Unpredictability of the Art and Amount of Experimentation. The art of using pharmaceuticals to inhibit enzymes is highly unpredictable as described by Kubinyi and shown in this context by Zhao. In nearly every case, the skilled artisan could not predict *a priori* whether a given pharmaceutical would inhibit an enzyme. When small variations in structure such as the addition of a methyl group has radical effects on the binding of an inhibitor, without specific guidance or correlations indicating how the structure of species affects its ability to inhibit an enzyme the scope of enablement is constrained to compounds showing substantial similarity to those actually demonstrated to be useful. Furthermore, there would be a huge amount of undue experimentation required in order to synthesize and screen the billions of compounds within the claimed scope.

Considering the above factors, the claims are clearly not enabled for the full scope of the compounds claimed. The examiner recommends either amending the claim scope to only those compounds closely resembling the compounds actually tested and disclosed in the specification or provide additional data and/or structural correlations to guide one of ordinary skill in the art to compounds possessing the asserted utility.

Conclusion

The claims are not in condition for allowance.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert Havlin whose telephone number is (571) 272-9066. The examiner can normally be reached on Mon. - Fri., 7:30am-5pm EST.

If attempts to reach the examiner by telephone are unsuccessful the examiner's supervisor, Joe McKane can be reached at (571) 272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Robert Havlin/
Examiner, Art Unit 1626